VERSION WITH MARKINGS TO SHOW CHANGES MADE

7. [The use of a sapogenin according to the formula recited in claim 1 in] A method of treating cancer cells in a human being suffering from cancer, [comprising] by killing the cancer cells, inducing apoptosis in the cancer cells, or inhibiting multiplication of the cancer cells, or any combination thereof, comprising administering to the human being a therapeutically effective amount of the sapogenin as claimed in claim 1.

8. [The use of a sapogenin according to the formula recited in claim 1 in] A method of treating multi-drug resistant cancer cells (MDR) in a human being suffering from cancer, comprising [using the sapogenins either singly] administering one or more of the sapogenins as claimed in claim 1, alone, or in combination with [one another, or in combination with] other chemotherapy agents.

16. The [cancer-treatment method of] method of treating cancer as claimed in claim 14 comprising a pharmaceutically effective amount of PAM-120, PAM-100 and PBM-110 with or without one or more pharmaceutically acceptable carriers, and one or more chemotherapeutic agents.

17. The [cancer-treatment method of] method of treating cancer as claimed in claim 14, wherein the active ingredient is administered in a dosage of between 5 micrograms to 50 grams per kg body weight per day.

18. The [cancer-treatment method of] method of treating cancer as claimed in claim 14, wherein the active ingredient is administered in a dosage of between [5o] 50 micrograms to 5 grams per kg body weight per day.

19. The [cancer-treatment method of] method of treating cancer as claimed in claim 17, wherein the form of the composition is selected from the group consisting of an orally administrable form, an injectable form, and a topically applicable form.

20. The [cancer-treatment method of] method of treating cancer as claimed in claim 19, wherein the orally administrable form is selected from the group consisting of a tablet, a powder, a suspension, an emulsion, a capsule, a granule, a troche, a pill, a liquid, a spirit, a syrup and a lemonade.

21. The [cancer-treatment method of] method of treating cancer as claimed in claim 19, wherein the injectable form is selected from the group consisting of a liquid, a suspension and a solution.

22. The [cancer-treatment method of] method of treating cancer as claimed in claim 19, wherein the topically applicable form is selected from the group consisting of a drop, a paste, an ointment, a liquid, a powder, a plaster, a suppository, an aerosol, a liniment, a lotion, an enema and an emulsion.

23. The [cancer-treatment method of] method of treating cancer as claimed in claims 14 or 15, wherein the composition is administered to human beings who are receiving one or more other anti-cancer treatments.

24. The [cancer-treatment method of] method of treating cancer as claimed in claims 14 or 15, wherein the composition is formulated with one or more other anti-cancer agents, for additive treatment effects, or synergistic treatment effects on multi-drug resistance cancers or any other cancer type.

REMARKS

35 USC 121 Restriction Requirement

The Examiner contends that the application is directed to more than one invention and has requested that the Applicant restrict the application to one invention. The Applicant elects to restrict the application to the invention claimed in claims 1 to 24, without prejudice to the Applicant's right to divide claims 25 to 32 and assert them in a divisional or continuation application.

35 USC § 101 Rejection

The Examiner has rejected claims 7 and 8 under 35 USC § 101 as the Examiner contends that they are not directed to statutory subject matter. The Applicant has amended claims 7 and 8 so that they are no longer directed to the "use" of sapogenin compounds as claimed in claim 1 for the treatment of cancer cells, but rather they are directed towards methods of treating cancer cells comprising administration of the sapogenin compounds as claimed in claim 1. The Applicant submits that these amendments should put the claims in condition for allowance and respectfully requests withdrawal of the rejection of claims 7 and 8.

35 USC § 112 Rejection

The Examiner has also rejected claims 16 to 24 under 35 USC § 112 as being indefinite. The Examiner contends that the term "cancer treatment method" used in these claims has no antecedent. The Applicant has amended these claims so that they are now directed towards a "method of treating cancer" which has an antecedent in claim 14, and claims 16 to 24 directly or indirectly depend from claim 14. The Examiner has also rejected claims 17 and 18 because the term "active ingredient" in these claims also has no antecedent in claim 14. The Applicant has replaced the term "active ingredient" with the term "composition" which does have an antecedent in claim 14. The Applicant has also corrected a typographical error of the numeral "50" in claim 18. The Applicant submits that these amendments should put the claims in condition for allowance and respectfully requests withdrawal of the rejection of claims 16 to 24.

35 USC § 103 Rejection

The Examiner has rejected claims 1 to 24 under 35 USC § 103(a) as being obvious in light of Japanese Abstract No. JP08291194 issued to Hideo (Hideo) and PCT Publication No. WO 97/31933 issued to Park (Park). On page 6 of the Examiner's Report, the Examiner has asserted that Hideo and Park disclose compounds which differ from the compounds claimed in the application in the position of the double bond in the side chain at position 17. The Examiner has asserted that the compounds claimed in the application are positional isomers of the prior art compounds in Hideo and Park. Because Hideo and Park teach the use of dammarane sapogenins or saponins as anticancer and antitumor agents, the Examiner contends that one having ordinary skill in the art in search of additional sapogenins or saponins would be motivated to isolate or prepare the compounds as claimed in the application and expect them to have anticancer activity. The Applicant respectfully submits that the compounds of the invention are not obvious in light of the prior art and requests withdrawal of the rejection of claims 1 to 24 in light of the following.

First, the Applicant submits that <u>not all</u> of the compounds of the invention are positional isomers of the compounds disclosed in the cited prior art. It is submitted that the pairs of compounds which may be considered to be positional isomers are dammara-20(22),24-diene-3β,12β-diol, disclosed in Hideo (compound hereafter referred to as "J1"), and PAM-120; dammara-20(22),24-diene-3β,6α,12β-triol, disclosed in Hideo (compound hereafter referred to as "J2") and PBM-110, disclosed in the Application; and Δ20(22)-ginsenoside

Rg3, disclosed in Park (compound hereafter referred to as "P2"), and PAN-30 disclosed in the Application.

It is submitted that the remaining compounds of the invention are not positional isomers of the compounds disclosed in the cited prior art. The compound PBM-100 is not a positional isomer of J1 because PBM-100 has additional hydroxyl groups at positions 6 and 24. PBM-100 is not a positional isomer of J2 because PBM-100 has an additional hydroxyl group at position 24. PBM-100 is not a positional isomer of P2 because PBM-100 contains additional hydroxyl groups at positions 6 and 24, and there is a hydroxyl group at position 3 rather than a chain of glucosyl groups.

The compound PAN-20, disclosed in the application, is not a positional isomer of either J1 or J2 because PAN-20 has a single glucosyl group attached at position 3 but J1 and J2 have a hydroxyl group at that position. PAN-20 is not a positional isomer of P2 because there is only one glucosyl group attached at position 3, rather than a chain of glucosyl groups.

In addition to the compound P2, Park also discloses the compound 3β,12β-dihydroxy-damar-20(22),24-diene-3-O-β-D-6"-O-acetyl-glycopyranosyl-(1-2)-β-D-glucopyranoside (compound hereafter referred to as "P1"). The Applicant submits that because this compound contains an acetyl group attached to the chain of glucosyl groups at position 3, this compound is not a positional isomer of any of the compounds of the invention as none of the compounds of the invention are acetylated. Park also discloses the compound 3β,12β,20β-trihydroxy-damar-24-ene-3-O-β-D-6"-O-acetyl-glycopyranosyl-(1-2)-β-D-glucopyranoside (compound hereafter referred to as "P3") and the compound ginsenoside Rg3 (compound hereafter referred to as "P4"). The Applicant submits that because P3 also has an acetyl group attached to the chain of glucosyl groups at position 3, this compound is not a positional isomer of any of the compounds of the invention. The Applicants submits that compound P4 is not a positional isomer of any of the compounds of the invention because, unlike the compounds of the invention, P4 has no double bonds at position 20, and P4 has a hydroxyl group attached to position 21.

Therefore, the Applicant respectfully submits that the compounds PBM-100 and PAN-20 of the invention are not positional isomers of any of the compounds disclosed in the cited prior art. On page 6 of the Examiner's Report, under the heading "2. Ascertaining the differences between the prior art and the claims at issue", the Examiner contends that the "instant invention is considered obvious over the prior art, because instant invention is the positional isomer of the prior art." Because compounds PBM-100 and PAN-20 are not

positional isomers of the compounds disclosed in the cited prior art, the Applicant submits that these compounds are not obvious in light of the cited prior art. In addition, the Applicant submits that PBM-100 and PAN-20 are sufficiently different from the cited prior art compounds that they are not obvious in light of the cited prior art. Therefore, the Applicant requests that the Examiner withdraw the rejection of claims 3, 5, 10, and 12 which are directed to compounds PBM-100 and PAN-20.

Furthermore, even if the compounds of the invention are positional isomers of the cited prior art compounds, the Applicant submits that the mere existence of positional isomers in the prior art cannot be relied upon as the basis of an obviousness rejection. As explained in the case of *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal*, 231 F. 3d 1339 at 1343 (Fed. Cir. 2000), citing *In re Dillon*, 919 F.2d 688 at 692 (Fed. Cir. 1990), "For a chemical compound, a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter...where the prior art gives reason or motivation to make the claimed compositions'." The Applicant submits that the cited prior art does not give reason or motivation to make the compositions of the invention and therefore a *prima facie* case of obviousness cannot be established.

The Applicant submits that Park does not teach, suggest, motivate, or give reason for a person skilled in the art to make the compositions of the invention. Park discloses methods for creating acetylated ginseng compounds from non-acetylated ginseng compounds. However, none of the compositions of the invention contemplate acetylation. In addition, nowhere does Park teach or suggest alteration of the non-acetylated ginseng compounds into other non-acetylated ginseng compounds. Park arguably teaches away from the compounds of the invention because Park only teaches modification by acetylation and such modification would not create isomers of the non-acetylated ginseng compounds. Therefore, a person skilled in the art would not be motivated by Park to create the compounds of the invention.

The Applicant submits that Hideo does not teach, suggest, motivate, or give reason for a person skilled in the art to make the compositions of the invention. Although Hideo discloses compounds that may be structurally similar to the compounds of the invention, Hideo does not teach the conversion of those compounds into the compounds of the invention. Morever, the Applicant submits that it is known in the art that the chemical activity of a ginseng compound cannot be reliably predicted based on the activity of an isomer of that compound. Therefore, a person skilled in the art would not be able to

reliably predict that the compounds of the invention would have chemical activities similar to the activities of the compounds disclosed in Hideo.

In support of its submissions, the Applicant submits the article "Metabolism of 20(S)- and 20(R)-ginsenoside Rg3 by Human Intestinal Bacteria and Its Relation to *In Vitro* Biological Activities"(Bae et al., Biol. Pharm. Bull. 25(1)58-63 (2002)). This article discloses the results of experiments which compare the activity of the stereoisomers 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3. The authors demonstrated that the compound 20(S)-ginsenoside Rg3 was metabolised by human intestinal microflora at a greater rate than the compound 20(R)-ginsenoside Rg3 was metabolised. The transformation rate for 20(S)-ginsenoside Rg3 was 0.57 ± 0.20 nmol/h/mg wet weight of feces, while the transformation rate for 20(R)-ginsenoside Rg3 was only 0.03 ± 0.002 nmol/h/mg wet weight of feces. The authors also demonstrated that bacteria isolated from human feces were capable of hydrolyzing 20(S)-ginsenoside Rg3. The compound 20(R)-ginsenoside Rg3 was either hydrolyzed at a slower rate than 20(S)-ginsenoside Rg3 was hydrolyzed, or it was not hydrolyzed at all by the same bacteria. Moreover, 20(S)-ginsenoside Rg3 was found to exhibit greater toxicity on tumor cell lines than 20(R)-ginsenoside Rg3 was. 20(R)-ginsenoside Rg3 only exhibited weak cytoxicity on tumor cell lines. The Applicant submits that these differences in biological activity between the stereoisomers of 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 indicate that biological activity may not be reliably predicted in a ginseng compound by analyzing the activity of an isomer of the ginseng compound.

In the recent case of *Ex parte Bonfils*, 64 USPQ 2d 1456 (27 August 2002), the Board of Patent Appeals and Interferences held that a *prima facie* case of obviousness under 35 USC 103 will not be established for a claimed compound if the Examiner only relies on the disclosure of the stereoisomer of the claimed compound as the basis of the rejection. The Examiner must explain why the differences would have been obvious, and the explanation must be supported by evidence on the record. The Board of Patent Appeals held that "where, as here, there is evidence of ***unpredictability*** and no evidence of common pharmaceutical or biological properties, the 'presumed' expectation of similar properties due to the similar structures is not well-founded" (emphasis added).

In the case of *In re O'Farrell*, 853 F.2d 894 at 903 (Fed. Cir. 1988), the court held that even if there is motivation in the prior art to try an experiment, if the prior art only makes the particular experiment or modification "***obvious to try***," this motivation will also not

support a finding of obviousness. Furthermore, the prior art also needs to offer a "***reasonable expectation of success***" (*In re Longi*, 759 F.2d 887 at 896 (Fed. Cir. 1985).

The Applicant submits that the Examiner has only cited the disclosure of isomers of the compounds of the invention in the prior art, but the Examiner has not indicated how the cited prior art would motivate a person skilled in the art to try the compounds of the invention . The Applicant submits that, as evidenced by the article by Bae et al., it is known in the art that the activity of a ginseng compound may not be reliably predicted based on the activity of isomer of the compound. Therefore, even if there is any motivation in the prior art to make and test the compounds of the invention, the Applicant submits that this motivation would merely be a motivation to try the compounds. Moreover, because the cited prior art does not teach, suggest, or motivate a person skilled in the art to even try the compounds of the invention, the cited prior art cannot offer a reasonable expectation of success. The Applicant submits that the cited prior art cannot support a finding of obviousness.

The Applicant submits that even if the cited prior art compounds have chemical structures similar to the compounds of the invention, the differences between the compounds are significant and it would be difficult to predict the activity of one compound by examining the activity of its isomer. The Applicant submits that J1 and PAM-120, which may be considered positional isomers, differ from one another in the position of the double bond at position 20. In J1, the bond is between positions 20 and 22. In PAM-120, the bond is between positions 20 and 21. A double bond is a planar bond and does not rotate. As a result, in J1, the side chain attached at position 22 does not rotate, but in PAM-120, the side chain at position 22 can rotate. This flexibility in the side chain may result in different physical and stereochemical interactions between PAM-120 and a target molecule as compared to J1 and a target molecule. The Applicant submits that J2 and PBM-110, which may be considered positional isomers, differ from one another in the orientation of the side chain at position 22. PBM-110 is the trans molecule and J2 is the cis molecule. The difference in the orientation of the side chain at position 22 is significant because it may affect physical and stereochemical interactions between the side chain and target molecules. The differences in activities of cis and trans molecules can be unpredictable. The Applicant submits that P2 and PAN-30, which may be considered positional isomers, also differ from one another in the orientation of the side chain at position 22. PAN-30 is the trans molecule and P2 is the cis molecule. Again, the difference in the orientation of the side chain at position 22 is significant because it may affect physical and stereochemical interactions between the side chain and target molecules, and the affect can be

unpredictable. The Applicant submits that the unpredictability in activity of the isomers rebuts a finding of obviousness.

In support of the Applicant's submissions concerning the unpredictability of activity between isomers of ginseng compounds, the Applicant submits the affidavit of F. Geoffrey Herring, a professor in the Department of Chemistry at the University of British Columbia, Canada, pursuant to 37 CFR § 1.132. The affidavit is enclosed herewith.

In summary, the Applicant submits that not all of the compounds of the invention are positional isomers of the cited prior art compounds and therefore, the claims directed to these compounds cannot be considered obvious in light of the cited prior art. Even if the compounds of the invention are positional isomers of the cited prior art compounds, the Applicant submits that there is no motivation in the prior art to produce the compounds of the invention and therefore, the claims directed to the compounds of the invention are not obvious. Moreover, even if the prior art contained motivation to produce the compounds of the invention, the Applicant submits that it would merely be an "obvious to try" motivation to produce the compounds. The Applicant submits that it is known in the art that the activity of a ginseng compound may not be reliably predicted based on the activity of an isomer of the compound. Therefore, there is no "reasonable expectation of success" offered by the prior art to support a finding of obviousness. Lastly, the Applicant submits that even if the cited prior art compounds are positional isomers of the compounds of the invention, there are significant differences between the compounds such that the activity of one compound cannot be reliably predicted based on the activity of the isomer of that compound. Therefore, a finding of obviousness is not supported by the cited prior art.

In light of the foregoing, the Applicant respectfully requests that the Examiner withdraw the obviousness rejection from claims 1 to 24 and allow the application.

Respectfully submitted,

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